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Publisher's Letter

I find myself in a time of reflection. I am celebrating my 25th wedding anniversary, as well as 24 years in the natural health product industry! As these celebrations unfold I think about how both the industry and I have matured over time. One of the greatest joys I have experienced professionally is being able to participate in the growth of many talented practitioners and researchers in our wonderful industry.

It truly is the practitioners and researchers that drive our industry forward, and without their passion and dedication publications like CJNM would not exist. I find myself reflecting on the amazing progress our industry has made over the past 24 years. When I first began, research focused on natural health product ingredients was sparse. The past two decades has seen an explosion in research focused on our industry. Dedicated practitioners assimilate the evidence to help guide clinical practice, and us retailers benefit from knowing that the ingredients we carry indeed deliver important health outcomes when used appropriately. Given the incredible growth and validation our industry has enjoyed over the past 24 years I am confident the future of our industry is indeed bright – the natural health products industry is an important contributor to the health care system, and we are here to stay.

I personally want to thank all of our Authors and Referees, Dr Rouchotas, Dr Peter Jones and companies like NFH in supporting the growth and maturity of the natural health products industry. If not for their tireless efforts CJNM would never have been possible! Thank you!

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Editor's Letter

COVID messed up many things. Of note in our home was organized sports. Our children were just beginning to join sports teams when the pandemic hit, and for two years this aspect of life was put on pause. Yet now it is in full swing and I am embracing the role of taxi driver/cheerleader as best I can. I suddenly find myself wondering how my parents managed two boys in competitive sports? I am finding two young children in non rep sports a full-time job. It sure is refreshing to see sports fields filled with children again.

I hope our readership is having the opportunity to embrace summer and top up their vitamin G levels! Whether it's a cottage, a hike, or a stroll, it's the time of year to get outside!

I thank our Authors and our Referees for delivering the June 2022 issue of CJNM. Dr Botsford assimilates expert advisory recommendations from multiple sources and combines them into one comprehensive resource of guidance for return to play following COVID infection among athletes. Dr McKinney takes a deep dive into molecular happenings in cancer showcasing opportunities for intervention. Dr Shapoval has found important early-stage human evidence of intervention with various natural health ingredients for optimization of epilepsy management. Dr Fernandes updates evidence of omega-3 fatty acids across an array of common mental health concerns. Dr Del Duca and colleagues introduce the profession to ultrasound guided injection therapy for pain management, showcasing jurisdictions across North America allowing ND's to perform such procedures. Riley Forbes and I have partnered to deliver a review of antiviral efficacy of green tea, including a handful of trials that have evaluated green tea specifically for prevention and treatment of COVID.

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Canadian Journal of Naturopathic Medicine

Clinical Guidelines for Return to Play Following COVID-19 Infection

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The Author declares a role in research and product development with F2C Nutrition

Clinical Guidelines for Return to Play Following COVID-19 Infection

Abstract

The emergence of COVID-19 has impacted all areas of clinical practice, and to those working with elite athletes pose some unique challenges. Return to play (RTP) following an illness has received considerable research interest over the years, yet COVID-19 has forced consideration of strategies to govern safe RTP from a novel virus for which many unknowns remain. Cardiopulmonary complications seen with COVID-19 infection require careful consideration and thorough clinical evaluation to ensure RTP is conducted in a safe manner. Several advisory panels have convened and set forth guidelines to govern RTP for athletes following COVID-19 infection. This review will assimilate the recommendations of these various advisory panels and attempt to consolidate a practical comprehensive set of recommendations clinicians can call upon to minimize potential harms associated with athletic performance following COVID-19 infection.

Introduction

Working in primary care, naturopathic doctors encounter athletic patients who have experienced a COVID-19 infection. Patients that compete in a sport and/or exercise with the intent of improving their performance can be defined as athletes. Vasiliadis and Boka (2021) defined athletes as those fulfilling the following three criteria: intent of the exercise, participation in sport events, and registration in a sports federation. For the purposes of this article, the last criterion is not recommended to define an athlete as it excludes patients that may require guidance about return to exercise post infection. Several publications exist suggesting a variety of guidelines for return to play (RTP) protocols after COVID-19 infection (Gluckman et al 2022, Elliott et al 2020, Halle et al 2021, Nieß et al 2020, Vasiliadis and Boka 2021). The aim of this article is to assist clinicians in simplifying the variety of recommendations into a concise, easily applied clinical tool.

Return to Play (RTP) Guidelines

In the current guidelines for RTP protocols post COVID-19 infection in athletes, the biggest variability is in the objective measurements (lab testing, imaging, and other investigations) that are recommended prior to graded return to sport. Earlier publications suggest more investigations including cardiac magnetic resonance imaging (CMR), electrocardiogram (ECG), and echocardiography, likely due to the paucity of available information about severe complications arising from mild or moderate COVID-19 infection (Halle et al 2021, Vasiliadis and Boka 2021). Later publications propose fewer objective investigations to guide RTP protocols (Casasco et al 2022, Gluckman et al 2022) likely due to the relatively unlikely occurrence of severe complications such as myocarditis in athletes not experiencing cardiac symptoms (Modica et al 2022). In a systematic review and meta-analysis of available literature studying athletes recovered from COVID-19, the event rates for myocarditis in the athletic population ranged from one to 4% (Modica et al 2022).

Athletes with severe COVID-19 infection requiring hospitalization should be followed by a multidisciplinary team to determine individualized RTP with exercise rehabilitation specialists (Casasco et al 2022, Gluckman et al 2022, Vasiliadis and Boka 2021) and are beyond the scope of this document. Patients with self-limiting COVID-19 infection, including those who are asymptomatic, or have mild or moderate symptoms without cardiac involvement, are included in the guidelines proposed.

Upon testing positive for COVID-19, an athlete should rest until symptoms resolve (Elliott et al 2020). The British Journal of Sports Medicine (BJSM) infographic for RTP, originally published in October 2020, recommends a minimum of 10 days rest (Elliott et al 2020), however updated guidelines indicate that athletes with mild or moderate non-cardiopulmonary symptoms can resume exercise after their symptoms resolve (Gluckman et al 2022). Another set of guidelines recommends the introduction of low-intensity exercise 72 hours after the resolution of symptoms, citing that high-intensity exercise may increase the risk of upper respiratory tract infection and/or complications while low-to-moderate intensity exercise may improve immune

function (Vasiliadis and Boka 2021). The authors did not define high or low-intensity exercise based on an objective measure, making this guideline difficult to apply practically. The BJSM infographic recommends the athlete be able to participate in the activities of daily living (e.g. walk 500m) without aggravating respiratory symptoms or causing excessive fatigue prior to initiating their graduated RTP protocol. They also clearly define their RTP recommendations with objective heart rate measures (Elliott et al 2020). In an asymptomatic athlete who has tested positive for COVID-19, the guideline is exercise abstinence for three days (Gluckman et al 2022). One important consideration in RTP guidelines is that longer periods of physical inactivity may increase the risk of injury (Gluckman et al 2022, Puga et al 2022). Guidelines need to balance cardiopulmonary event risk and injury prevention.

The overall risk of myocarditis following COVID-19 infection in otherwise healthy athletes appears to be relatively low with studies citing an event rate of one to 4% (Modica et al 2022). A large multicentre Italian study of 4000 athletes who tested positive for COVID-19 from a variety of sport disciplines included objective cardiovascular measurements in their RTP protocol (Casasco et al 2022). This study used the NIH classification for COVID-19 patients, separating athletes into three categories by severity of disease. Professional athletes were included in the most severe category regardless of symptomatology and received more investigations than non-professional athletes. Mildly symptomatic patients received a 12-lead ECG at rest and during maximal exercise with continuous O2 saturation monitoring and an echocardiogram. Moderately symptomatic individuals and those requiring hospitalization received the previous investigations in addition to a 24 hour ECG on a training day and CMR. Professional athletes and those with severe/critical disease received all previously mentioned investigations in addition to a cardiopulmonary exercise test. Additional testing was on a case-by-case basis determined by the sports medicine doctors and included but was not limited to pulmonary imaging and CMR. All athletes in the study received blood work including complete blood count, liver function tests, kidney function tests, lactate dehydrogenase, clotting factors, protein electrophoresis, d-dimer, and ferritin testing. With this extensive monitoring of a variety of athletes, cardiac complications were very rare: myocarditis was detected in 0.12% of the total population, and a variety of arrhythmic events were the most common finding (Casasco et al 2022). The authors concluded that safe RTP may include an ECG-monitored exercise test, but they do not propose a schedule for returning to exercise (Casasco et al 2022).

Other guidelines also recommend objective screening measures in athletes returning to exercise post-infection including ECG, c-reactive protein (CRP), creatinine, complete blood count, and creatine kinase (Halle et al 2021). If all findings are normal, the authors suggest returning to exercise gradually after two weeks of complete clinical recovery. The graded return should be two to three days for each training day lost to illness (Halle et al 2021). Practically, this guideline agrees with both the American College of Cardiology Consensus Statement and the Infographic published by the BJSM (Gluckman et al 2022, Elliott et al 2020); In the case of an athlete who is

symptomatic with COVID-19 infection for five to seven days, a graduated RTP would be approximately 10-15 days (Halle et al 2021).

Adverse cardiac event outcomes appear to be relatively low in athletes in their recovery from COVID-19 infection (Casasco et al 2022, Modica et al 2022). A study looking at total injuries in the 2020 National Football League Season showed muscular-skeletal injury risk may increase following a reduction in training time (Puga et al 2022). A study based on a survey of competitive runners suggests that runners that reported having COVID-19 have a slightly higher incidence of injury compared to those that did not have COVID-19 (Toresdahl et al 2022). It is unclear if COVID-19 infection causes pathophysiologic changes that increase the likelihood of injury, but it is possible that reduction in training load combined with lack of graduated RTP may be a risk factor for injury (Puga et al 2022, Toresdahl et al 2022).

A graduated RTP protocol is recommended for all athletes suffering a COVID-19 infection, regardless of severity of symptoms. To pool and summarize the available evidence, the following schedule is recommended:

A. Initial Rest: Minimum five days, until complete symptom resolution
    a. Athletes must tolerate activities of daily living without excessive fatigue or respiratory symptoms prior to moving to step B
    b. Athletes tolerating activities of daily living may integrate range of motion activities into their daily routine
    c. Athletes experiencing cardiac symptoms should be referred to undergo screening including ECG
B. Introduction of Exercise: Duration 15 minutes, less than 70% of heart rate maximum
    a. This may include sport specific drills and skills
    b. Athletes should stay at this phase for a minimum of one day
    c. Athletes must not experience any excessive fatigue or return of any symptoms following their effort prior to moving to the next phase
C. Increased Intensity and Duration: 30 minutes of activity, less than 80% of heart rate maximum
    a. May include normal training activities, but duration and intensity remain limited
    b. Minimum two days
    c. Athletes must not experience any excessive fatigue or return of any symptoms following their effort prior to moving to the next phase
D. Increased Duration: 45 minutes, less than 80% of heart rate maximum
    a. May include normal training activities, but duration and intensity remain limited
    b. Minimum two days
    c. Athletes must not experience any excessive fatigue or return of any symptoms following their effort prior to moving to the next phase
E. Resume all normal training activities

Discussion

The above suggested protocol is a minimum of 10 days but may be longer depending on an individual athlete's progression. Athletes should be educated about the possibility of increased injury risk following a period of convalescence as well as the importance of seeking care for any

cardiac symptoms. Clinicians can reassure athletes that adverse cardiac event risks are relatively low and that a graduated RTP may reduce the risk of injury and/or other adverse events. This guideline is limited by the evolving understanding of COVID-19 and possibly long-term consequences of this relatively novel virus. As more data emerge there will likely be changes to our RTP protocols. Conservative and graduated RTP is most responsible to mitigate injury risk, despite the relatively low risk of cardiac complications of COVID-19.

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Opportunities in the Metabolic Chaos of Cancer

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Opportunities in the Metabolic Chaos of Cancer

Abstract

Cancer cells demonstrate the Warburg Effect. They ferment fuel by anaerobic glycolysis despite the presence of oxygen. This remarkable metabolic transformation at the onset of malignancy appears to be an innate adaptation to hypoxia. Cancer cells always continue some oxidative phosphorylation, and will die in a completely anoxic environment, but adapt to a crowded, compressed, and hypermetabolic situation by moving almost entirely to a metabolic phenotype that can operate without oxygen. Fermentation is not just an alternative way to obtain cellular energy - it provides increased biosynthesis of cellular components necessary to maintain exponential tumour growth. Anaerobic glycolysis is also a route to epigenetic alteration of the phenotype. Increased *de novo* synthesis includes not only structural cellular components, but also signaling molecules such as succinate that interact with both oncogene and tumour suppressor pathways. The mitochondria reprogram the cancer cell genetics to a new fermentative, fetal-like phenotype characterized by symmetrical mitosis. Targeting fermentation by cancer cells appears to have huge potential for healing and preventing cancer. Tumour growth and spread is linearly related to loss of, and damage to cancer cell mitochondria. Restoring mitochondria numbers and polarization, with redirection of cellular bioenergetics back towards oxidative phosphorylation, is possible. This tactic should result in lower rates of disease progression, invasion, metastasis, and relapses, particularly in common and deadly cancers which are grossly fermentative, such as of the breast, pancreas, liver, and colon.

Introduction

Cancer cells demonstrate the Warburg Effect (Koppenol et al 2011, Warburg 1956) – they ferment fuel by anaerobic glycolysis despite the presence of oxygen. This remarkable metabolic transformation at the onset of malignancy appears to be an innate adaptation to hypoxia. Surgeries and traumas create hypoxic zones. The Standard American Diet (SAD) creates a significant net acid residue compared to ancestral diets, reducing cytoplasmic oxygen retention (Frassetto et al 2001, Pizzorno 2012). Cancer cells always continue some oxidative phosphorylation, and will die in a completely anoxic environment, but adapt to a crowded, compressed, and hypermetabolic situation by moving almost entirely to a metabolic phenotype that can operate without oxygen. Reduced perfusion creates relative hypoxia, and the resulting shift to glycolytic metabolism (Fang et al 2008) generates high acid residue, which interacts with the pH gradient and resulting voltage gradient in mitochondria when moving protons necessary for ATP production by oxidative phosphorylation (Lewis et al 2002), reinforcing the adaptation to the hallmark cancer cell dependence on anaerobic glycolysis. Fermentation is not just an alternative way to obtain cellular energy, it provides increased biosynthesis of cellular components necessary to maintain exponential tumour growth and is a route to epigenetic alteration of the phenotype. Increased *de novo* synthesis includes not only structural cellular components, but also signaling molecules that interact with both oncogene and tumour suppressor pathways (Röhrig and Schulze 2016). The mitochondria reprogram the cancer cell genetics to a new fermentative, fetal-like phenotype (Seyfried 2012, Wallace 2012).

Targeting fermentation by cancer cells appears to have huge potential for healing and preventing cancer (Abdel-Wahab et al 2019, Bucay 2007, Frezza and Gottlieb 2009, Gogvadze et al 2008, Hanahan and Weinberg 2000, Hanahan and Weinberg 2011, Kulawiec et al 2009, Vander Heiden et al 2009, Wallace 2005, Yeung et al 2008). Tumour growth and spread is linearly related to loss of, and damage to, cancer cell mitochondria (Christofferson 2014). The landmark dichloroacetate (DCA) study of 2007 from the University of Alberta showed that restoring the malignant cell mitochondrial membrane potential can spark up oxidative metabolism, and this will arrest tumour growth (Bonnet et al 2007). Restoration of mitochondrial respiration must also influence the retrograde signaling and epigenetic reprogramming of cancer cells. This normalization of cellular bioenergetics should result in lower rates of disease progression, invasion, metastasis, and relapses, particularly in common and deadly cancers which are grossly fermentative, such as of the breast, pancreas, liver, and colon.

Possible Opportunities for Impacting Cancer Cell Metabolism

The number of cells in a given tissue remains constant once in the second trimester of gestation. Normal cells follow a mature growth pattern whereby cells do not reproduce, but if lost, are replaced from stem cells, in a process called asymmetrical mitosis. The stem cell makes a functional replacement differentiated cell, plus a new stem cell for future use. Cancer cells are reprogrammed to behave like the earlier fetal cells, with symmetrical mitosis generating masses of relatively undifferentiated cells. Cancer cells with this unlocked mitotic potential arise from a

multitude of factors, such as radiation-induced mutations and DNA damage, toxic exposure such as to heavy metals (e.g. cadmium), or from bioactive chemicals such as pesticides. Inherited defects in DNA repair and other genetic issues account for perhaps 10% of cases. The Standard American Diet (SAD) leads to a dramatic increase in acid load and profound alterations in the sodium-potassium ratio (Frassetto et al 2001, Pizzorno 2013), which alters oxygen capacity of the cytoplasm. Mitochondrial and endoplasmic reticulum nutrient sensors adapt with changes to mitochondrial membrane function (Arnett 2010, De Saedeleer et al 2012, Fang et al 2008, Lemasters and Holmuhamedov 2006, Pizzorno 2012, Robey 2012). Mitochondria are also more sensitive and less able to repair DNA damage from most drugs and toxic substances (Cohen 2010, Darlington 1948). Cancers always have mitochondrial damage (Jurasunas 2006, Okouoyo et al 2004, Singh 2004, Varga et al 2015). The degree to which any cancer grows and spreads has a linear relationship to the number of lost or damaged mitochondria, and the shift to an increasing dependence on fermentation – burning fuel without oxygen (Christofferson 2014). Seyfried (Seyfried 2012, Seyfried et al 2014, Seyfried 2015, Seyfried et al 2017) and others have demonstrated that mitochondria are able to send retrograde signals to the nuclear DNA, reprogramming metabolism (Caino and Altieri 2016, Cerella et al 2015, Hung et al 2010, Ishikawa et al 2008, Jose et al 2011, Kaipparettu et al 2013, Ralph et al 2010, Wallace 2012). While anaerobic glycolysis is distinctly inferior to aerobic metabolism in terms of ATP energy production per molecule of fuel such as glucose, the cancer cells end up with normal amounts of energy by adaptations such as recruiting stromal cells to make ATP, a process called the Reverse Warburg Effect (Feron 2009, Sotgia et al 2011, Sotgia et al 2012).

Accumulation of succinate is a key aspect of metabolic dysregulation in carcinogenesis. This buildup of a Krebs cycle metabolite inhibits several α-ketoglutarate dioxygenases, thereby inducing a pseudohypoxia pathway (Teicher et al 2012), and via hypoxia inducible factors HIFαand HIF β, causes epigenetic reprogramming of genes regulating energy metabolism, angiogenesis and cell survival. Loss of succinate dehydrogenase enzyme (SDH) (aka Complex II) leads to reprogramming of cell metabolism to support glycolysis. Mutations of genes encoding for the succinate dehydrogenase complex are associated with familial paraganglioma, pheo-chromocytoma, renal cell carcinoma, gastrointestinal stromal tumors and, possibly, pituitary adenomas. SDHx-related tumors display the Warburg effect, driven by HIFα, which induces expression of GLUT1 and GLUT3, hexokinase 2, pyruvate kinase variant M2 (PKM2) and lactate dehydrogenase A (LDH-A), thereby stimulating the shift from oxidative phosphorylation to glycolysis. There is an overexpression of LDH-A which converts pyruvate to lactate, thereby recovering the NAD+ needed to maintain glycolysis, critically important for tumor proliferation. Inhibitors of GLUT1, pyruvate dehydrogenase kinase (eg DCA), and pyruvate carboxylase are potential targets for treatment of SDHx-associated tumors (Eijkelenkamp et al 2020). SDHx also triggers the epithelial to mesenchymal transition, cell migration and invasion (Dalla Pozza et al 2020). Anti-inflammatory tumour-associated macrophages (TAMs) secrete cytokine TGF-β that suppresses the transcription factor STAT1,

decreasing the production of succinate dehydrogenase (SDH) enzyme in breast cancer cells (Gomez et al 2020). Melatonin may inhibit succinate accumulation (Gu et al 2020).

Central to the shift to a malignant phenotype is the down-regulation of phosphatases that dampen reactions and the up-regulation of kinases that stimulate metabolism and growth. The key metabolic controller pyruvate dehydrogenase kinase (PDK) creates a biochemical bottleneck, with a shift towards fermentation (Luo et al 2011, Pathania et al 2009). Under hypoxic conditions oxidative phosphorylation (OxiPhos) can no longer convert pyruvate to acetyl-CoA via the tricarboxylic acid (TCA) cycle. Anaerobic glycolysis uses lactate dehydrogenase (LDH) pathway to convert pyruvate to lactate, and lactate to pyruvate (da Veiga Moreira et al 2021).

The other hallmark of the malignant cell metabolism is glutaminolysis, the burning of glutamine as a fuel to generate TCA metabolites such as citrate, glutamate, pyruvate, and lactate, for the production of nucleic acids and other important cellular components needed by the cancer cells. For example, citrate can be used to make acetyl-CoA, which is needed to produce *de novo* lipids. These fatty acids are used structurally, but also as signalling molecules acting on oncogenes and tumour suppressor pathways (Röhrig and Schulze 2016). Normal cells use hexokinase one (HK1 or Hex I) on the mitochondrial membranes to move glucose, but cancer cells also make the unique hexokinase two (HK2 or Hex II) in abundance. HK2 takes ATP and glucose and produces glucose-6-phosphate. This precursor to lactate serves to lock on the throttle of glycolysis. Not only does this shift in biosynthesis of cellular components increase cell proliferation, it inhibits apoptosis, effectively immortalizing the malignant cells (Mathupala et al 2006).

In a landmark study in 2007 at the University of Alberta, it was demonstrated that dichloroacetate (DCA), a simple chlorinated vinegar, could inhibit PDK and shift mitochondria in cancer cells back to oxidative phosphorylation (Bonnet et al 2007). Rather than this pyruvate mimetic (Stockwin et al 2010) “giving the cancer more energy” as might have been imagined, the result was a dramatic decline in cancer growth. Unfortunately, premature hype of DCA (Coghlan 2007) lead to many people being harmed by self-prescribing on DCA obtained over the internet, overdosing (no human dose had been determined), or from using fraudulent or contaminated products. The first controlled human trial of DCA for cancer in 2010 showed significant toxicity to the peripheral nervous system, limiting its utility to brain and neurological cancers, which it rapidly saturates (Michelakis et al 2010). A smattering of published case studies has demonstrated some positive outcomes (Khan 2011, Khan 2012, Khan et al 2014, Khan et al 2017). DCA is highly neurotoxic when taken by mouth (Cornett 1999, Felitsyn 2007, Kaufmann 2006, Stacpoole 1998, Schaefer 2006).

The mechanism of action of DCA:

DCA inhibits pyruvate dehydrogenase kinase, triggering an influx of acetyl-CoA into mitochondria. This drives more NADH into complex I. Superoxides that form are converted into hydrogen peroxide by manganese-super oxide dismutase. The H_2O_2 inhibits proton (H+) efflux, reducing mitochondrial membrane potential m, the proton-driving force → ATP. This opens the mitochondrial transition pore (MTP), inhibiting calcium ion entry via voltage-dependent channels. Reduced intra-mitochondrial calcium (Ca++) suppresses a tonic activation of nuclear factor of activated T-lymphocytes (NFAT). NFAT1 is a nuclear transcription activator, similar in action to activator protein 1 (AP-1) and nuclear factor kappa B (NF B). This reduces Kv1.5 expression, increasing potassium ion K+ efflux, reducing inhibition of caspases, and finally triggering cancer cell apoptosis (Bonnet et al 2007).

Fortunately, there are promising candidates for safer alternatives to DCA, as published in the first peer-reviewed paper on "mitochondrial rescue" as a potential cancer therapy (McKinney 2008), revised and republished in 2011 (McKinney 2011). The most important elements of this mitochondrial rescue protocol were R-alpha lipoic acid (ALA) (Abolhassani et al 2012, Baronzio et al 2012, Dörsam and Fahrer 2016) and thiamine - vitamin B1 (Babaei-Jadidi et al 2003, Comin-Anduix et al 2001). ALA activates pyruvate dehydrogenase (PDH) by inhibition of pyruvate dehydrogenase kinase (PDK), which results in an increased amount of pyruvate entering the tricarboxylic acid cycle. This drives the mitochondria towards oxidative phosphorylation and away from the Warburg effect anaerobic glycolysis on which cancer cells depend. Adjuncts to support R-ALA in normalizing the functionality of mitochondria include the Co-enzyme Q10 derivative PQQ (pyrroloquinoline quinone), thiamine derivative benfotiamine, acetyl-L-carnitine, grapeseed extract, and quercetin. Dr. Walter Lemmo's discovery that DCA given by IV route was far less toxic than by mouth (private communication) revealed the potential to use DCA safely on non-neurological cancers. Later it was found that DCA and R-ALA could also be safely ingested by inhalation using a nebulizer (McKinney 2020B, McKinney 2020C). This metabolic approach was tried in many patients with advanced cancer, or cancers not responsive to the standard of care, with some good responses, including in some cases rapid tumor shrinkage. However, these anecdotal reports have yet to be fully tested in controlled studies or published under peer-review.

As well as fixing the damaged mitochondria in the cancer cell, it is also possible to increase the number of mitochondria, known as mitogenesis. One tactic for increasing mitogenesis is to increase intracellular nitric oxide, which can be accomplished with grapeseed extract proanthocyanidins (Vitseva et al 2005). Another mitogenic tactic is to activate adenosine monophosphate kinase (AMPK) (Chaube and Bhat 2016), which we may achieve with aerobic exercise, resveratrol, curcumin, quercetin, metformin, berberine, or green tea EGCG (McKinney 2020B, McKinney 2020C). Mitogenesis will also increase if peroxisome proliferator-activated receptor (PPAR) gamma γ (Jamwal et al 2021) coactivator 1α (PGC-1α) is inhibited with fermented wheat germ extract (FWGE) or red wine. PGC-1α is a transcriptional coactivator of

the fusion mediator mitofusin-2, which is modulated by resveratrol. Also potentially effective would be increasing the levels of the "fountain of youth" sirtuin protein *SIRT1,* an NAD-dependent histone deacetylase, by caloric restriction, resveratrol, quercetin, or exercise (Archer 2013, Shigenaga and Ames 1993).

Another key part of the malignant mitochondrial metabolic puzzle is how to inhibit Hexokinase II (HK2 or Hex II), to further shift away from fermentation (DeWaal et al 2018, Mathupala et al 2006). HK2 binds to mitochondrial porin, redirecting mitochondrial ATP to phosphorylate glucose and driving glycolysis (Wallace 2005). Dr. Davis Lamson, ND, and others such as Israel and Schwarz in France put forward several candidate inhibitors, including hydroxycitrate from *Garcinia cambogia* (Guais et al 2012, Israel and Schaeffer 1988, Israel and Schwartz 2011, Schwartz et al 2010, Schwartz et al 2012, Schwartz et al 2013, Schwartz et al 2014). Clinical responses to hydroxycitrate have not been robust. In pre-clinical studies, lectins from Solomon's seal herb (*Polygonatum spp.*) strongly inhibit HK2 (Wang et al 2011, Zhang et al 2017) and GLUT2 (Wang et al 2018). The target lectins are most abundant in the leaf, explaining why the whole-herb extracts seem to be much more bioactive in oncology than the root extracts commonly used for arthritis. The bioflavonoid quercetin is also a candidate Hex II inhibitor (Graziani 1977). Itraconazole is an antifungal drug that is being repurposed as a Hex II inhibitor (Gu et al 2016).

Another opportunity to intervene in the fermentation phenotype in cancer is how it regulates the highly acidic and toxic lactate output. Lactate can behave as a hypoxia mimetic factor capable of activating transcription factor HIF-1 in normoxic cancer cells, a key step in angiogenesis (Koukourakis et al 2005, Koukourakis et al 2006), and in triggering cancer cells to develop stem cell properties by which they become virulently malignant. Lactate over-production has many negative consequences (Walenta et al 2000, Walenta et al 2004), including reducing tumour antigenicity to dendritic immune cells (Gottfried et al 2006). Cancer cells are distinctly more alkaline on the inside than normal cells of the same type (Hao et al 2018), although the environment right around them is highly acidic (Newell et al 1993). This localized pH stress is an obvious therapeutic target (Huber et al 2017, Martin et al 2012, McCarty and Whitaker 2010, Pilon-Thomas et al 2016) but one that has proven elusive to overcome in practice. Laypeople as well as doctors have assumed from a cursory view of Warburg's findings that a net alkaline residue diet, and alkaline therapies such as intravenous bicarbonate, will address this problem, but clinical results have been marginal (Martin et al 2012, Wenzel and Daniel 2004). Alkalizing increases patient quality of life but has little to no impact on progression of the disease. Rather than halting lactate production, or neutralizing it in the periphery of the tumour, it may be best to keep it in the cancer cell. In malignant cells there is a dramatic up-regulation of proton efflux pumps, shifting the acidic lactate from the cancer cell cytoplasm out into the pericellular spaces. This opens up the possibility of killing cancer cells by inhibiting these proton-coupled mono-carboxylate transporters, especially MCT1 and MCT4 (Benjamin et al 2018, Colen et al 2011, Payen et al 2020, Pérez-Escuredo et al 2016, Sun et al 2020). Quercetin appears to be the most

promising intervention to address this tactic (Batiha et al 2020, Jones et al 2017, Ikegawa et al 2002).

Ketogenic diets are a relatively new concept in cancer care (Harper and Drewery 2019, Katz and Edelson 2017, McKinney 2020A, McKinney 2020C, Poff et al 2015, Seyfried et al 2009, Winters et al 2017). Very high fat, moderate protein, and very low carbohydrate ketogenic diets take advantage of the ability of normal cell mitochondria to adapt to ketones as fuel, while cancer cell mitochondria cannot do so (Davis 2017, de Cabo and Mattson 2019, Khodabakhshi et al 2020, Lee and Longo 2011, Longo and Fontana 2010). Some possible adjuncts to the ketogenic diet are supplemental ketones such as β-hydroxybutyrate, acetoacetate or 1,3,butane-diol, Metformin, berberine, Poly-MVA™ lipoic acid-palladium complex, hyperbaric oxygen therapy, and vitamin A retinol (Anderson 2018, Stengler and Anderson 2018). Fasting was once a widely used tool for healing, and research is now returning this dietary intervention to the clinical practice. Fasting - near, full, or intermittent – positively influences tolerance of SOC (standard of care) oncology therapies, and increases survival, in part by destressing mitochondria (Lee et al 2010, Lee and Longo 2011, Longo and Fontana 2010, Lv et al 2014, Safdie et al 2009, Simone et al 2018).

Discussion

Cancer cells adopt a phenotype largely dependent on anaerobic glycolysis. The cell is epigenetically reprogrammed to a fetal growth pattern. Since the cell has once undergone a shift from the fetal growth pattern (symmetrical mitosis) to the mature normal cell replacement model (asymmetrical mitosis), it is possible a mechanism exists to move the cancer cell from symmetrical mitosis to the normal asymmetrical pattern. Mitochondria in cancer cells drive the metabolic shifts and retrograde signalling to the genome, and their numbers and functionality correspond to the aggressiveness of the disease. Since the aberrant metabolism of cancer cell mitochondria can be corrected, it suggests a possible path to actually healing the cancer cell. Natural medicine candidates with pre-clinical and limited clinical evidence demonstrating the ability to correct cancer cell metabolism and mitochondria include quercetin (Batiha et al 2020, Zhang et al 2005, Das et al 2020, Jones et al 2017, Kothan et al 2004, Langner et al 2019, Ikegawa et al 2002, Suolinna et al 1975), R-alpha lipoic acid (da Veiga Moreira et al 2021, Humphries and Szweda1998, Korotchkina et al 2004, Moffa et al 2019, Wenzel et al 2005), thiamine (Parkhomenko et al 1987, Sheline et al 2002), acetyl-L-carnitine (Hoang et al 2007, Wenzel et al 2005), phloretin (Abdel-Wahab et al 2019, Choi 2019, Tang and Gong 2021), grapeseed proanthocyanidins (Nguyen and Pandey 2019), Coenzyme Q10 (Berbel-Garcia et al 2004, Smith et al 2008), Solomon's seal (*Polygonatum spp*.) lectins, and blackseed (*Nigella sativa*) thymoquinone (Tavakkoli et al 2017). A ketogenic diet appears to be supportive of this positive metabolic shift, as does fasting.

Common clinical doses of candidate substances for metabolic regulation:

Acetyl-L-carnitine 1000mg tid.

Alpha lipoic acid 300mg bid R-ALA or 600mg bid if DL-ALA.
May also be administered by IV 150mg twice a week, or by nebulization 50-100mg bid.
Berberine 300-500mg bid Coenzyme Q10 – 300mg qd of ubiquinone or 100mg of ubiquinol.
Curcumin -120mg bid of TheraCurmin™ or bid water-soluble curcumin extract.
Dichloroacetate – IV up to 3000mg twice weekly, or nebulized 250mg up to bid.
Fermented wheat germ extract (FWGE) 9g qd – bid.
Grapeseed extract 250mg bid.
Hydroxycitrate from *Garcinia cambogia* 1000mg bid.
Phloretin 1000mg bid.
Quercetin 1000mg bid, less if in liposomal format, delivering up to 140mg bid of dihydroquercetin.
Red wine 1 glass daily.
Resveratrol 250mg bid.
Sodium bicarbonate – up to ½tsp bid.
Solomon's seal aerial herb *Polygonatum spp*. (minus seeds which are toxic) 5:1 tincture – 30 drops (½tsp) bid.
Thymoquinone, from blackseed *Nigella sativa*, 100-200mg bid.
Vitamin A retinol 25000IU retinol or 30000IU palmitate daily, but lower to 5,000IU if ALT or AST are over 300.
Vitamin B1 - 100-200mg bid as thiamine, or 160mg bid as Benfotiamine™.

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Epilepsy: Nutrients and Herbs

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Epilepsy: Nutrients and Herbs

Abstract

Epilepsy is a common neurological disorder that affects a large global population. While antiepileptic medications provide great relief, nearly 30% of cases remain insufficiently or completely unmanaged. There is a growing interest in the complementary and alternative care and a number of systematic reviews have explored the potential benefits of many herbs. Unfortunately, these reviews focused on preclinical data, comprised of animal and *in vitro* studies. This review will explore the latest clinical developments in the nutritional and herbal approaches for epilepsy, including *Paeonia officinalis, Ganoderma lucidum,* Vinpocetine, probiotics, melatonin, omega 3, vitamin E, vitamin D, N-acetylcysteine, and coenzyme Q10.

Introduction

Epilepsy is considered to be one of the most common neurological disorders worldwide (Beghi 2020), affecting 0.4 to 1% of the population of all genders, ages, and ethnicities (Kim and Cho 2019). Relapse with epilepsy is characterized by seizures that do not have an identifiable neurological trigger or precipitating factor and thus appear unprovoked. The classification of seizures is based on the onset of the abnormal activity. When seizures originate from one specific location of the brain they are termed as "focal" and if they begin in multiple locations spanning both hemispheres they are "generalized". Additional terms help to define whether the seizures begin with motor or non-motor symptoms and whether there is a change in awareness. These classifications are useful to describe the way that the seizures present, but do not dictate the mechanism by which they originate. Epilepsy is a disorder that encompasses a wide range of pathophysiological process that can stem from or be promoted by different conditions, including brain trauma/structural, post-stroke, cancers, autoimmune, infectious, metabolic, and genetic.

Management of epilepsy includes the use of antiepileptic drugs (AEDs) comprised of carbamazepine, levetiracetam, phenytoin, sodium valproate, clobazam, and others (Perucca et al 2018). These medications work to increase the seizure threshold and thus make it more difficult for the neurons to produce the synchronous spontaneous activity that results in seizures. Five main mechanisms of action have been frequently cited in the literature. These include: (1) activation of the GABA receptor, (2) inhibition of the AMPA receptor, (3) inhibition of calcium voltage gated channels, (4) inhibition of sodium gated channels, and (5) activation of voltage gated potassium channels. Additionally, oxidative stress and pro-inflammatory states have been observed in patients with epilepsy, but their direct connection to seizure generation is less clear. In certain cases, where the AEDs fail to effectively control the seizures, surgery may be an option. However, this is dependent on the ability to precisely locate the epileptogenic zone. Additionally, there is a lack of clear prognostic outcomes for surgery, which limits the number of patients that are willing to proceed with this option (West et al 2019). Approximately 30% of cases cannot be managed with the AEDs, either due to lack of drug efficacy or due to the severity of adverse effects (da Fonsêca et al 2019). Thus, there is a great need to find alternative treatment options to provide care for these patients. This review will explore the latest clinical developments in the nutritional and herbal approaches for epilepsy.

Paeonia officinalis

In an open label study, 30 pediatric patients with intractable epilepsy were provided with an extract of *Paeonia officinalis* in addition to their AEDs (Zangooei Pourfard et al 2021). Paeonia was delivered as a hydroalcoholic extract of Paeonia with dose of 20mg/kg administered twice per day. At the end of the study (four weeks), there was a statistically significant decline in seizure frequency, compared to baseline, with 36.7% of the group achieving a greater than 75% reduction in seizures ($p<0.005$). The mean duration of seizures was also reduced significantly ($p<0.05$). The greatest benefit appeared to be achieved within the first week of intervention, however, there was a continuous decline in both duration and frequency observed between 3rd

and 4th weeks. It is possible that with longer administration there may have been additional benefits, but this needs to be explored in future trials. Adverse events included restlessness and constipation.

Ganoderma lucidum

The reishi mushroom has been used in a diverse range of health conditions and it is of no surprise to find *Ganoderma lucidum* being applied to the treatment of seizures. An observational study reports the adjunct use of *Ganoderma lucidum* Spore Powder (GLSP) by 18 participants with epilepsy for eight weeks with a statistically significant reduction in seizure frequency compared to baseline ($p=0.04$) (Wang et al 2018). The GLSP was administered as 1g three times per day in addition to the participants' regular AED. The seizure frequency was 3.1 per week on average and declined to 2.4 seizures per week by the end of the eight-week period. The most commonly reported adverse events included stomach discomfort and nausea. Preclinical research on GLSP suggests it may inhibit calcium influx or calcium accumulation within hippocampal neurons as well as promote expression of neurotrophin-4. Neurotrophin-4 is a more potent version of the brain-derived-neurotrophic factor (BDNF) which has been observed to increase after seizures (Scharfman 2005). It is not clear whether BDNF promotes epileptogenesis or is elevated as a protective mechanism to heal the damaged induced by the seizures.

Vinpocetine

A double blind randomized controlled study of 87 participants with focal epilepsy compared the impact of adjunct vinpocetine to the use of placebo. All participants were given their regular AEDs and were followed for four weeks to establish a baseline of seizure activity. For the next four weeks they were given titrated doses of either placebo or vinpocetine with the goal of reaching a target dose of 2mg/kg per day. Once this dose was reached, the participants were followed for eight weeks and then reassessed. The use of vinpocetine resulted in significant reduction in seizure frequency compared to placebo ($p<0.0001$). Of the placebo group, 13% reported a 50% reduction in seizures, while in the vinpocetine group 69% reported a 50% reduction. Adverse events included headaches and diplopia (Garza-Morales et al 2019).

What is vinpocetine? It is a synthetic derivative of a naturally-found compound called vincamine which is first heated to produce apovincamine, and then modified into vinpocetine. This compound is found within *Vinca* species, including *Vinca minor*. Vinpocetine has many proposed mechanisms of action. It can block sodium channels, reduce calcium influx, and provide antioxidant activity (Bereczki and Feketa 2008). Additionally, it provides protection against hypoxic induced apoptosis and increases cerebral blood flow, which may be targeting some of the underling mechanisms contributing to seizures.

The dose that was used in this study seems high compared to those reported in some of the literature on the use of vinpocetine in stroke recovery. At 2mg/kg, the current study would be delivering 140mg of vinpocetine per day to a 70kg adult, while the clinical trials reviewed in the systematic review on ischemic stroke ranged from 30-40mg per day (Bereczki and Feketa 2008).

Probiotics and Antibiotics

The importance of the gut microbiome is becoming apparent in an increasing number of neurological disorders. In the case of epilepsy, the hypothesis is that gut dysbiosis may be responsible for reducing the effectiveness of the AEDs (Chatzikonstantinou et al 2021). Microbial studies of the gut of patients with refractory or drug-resistant epilepsy, specifically their stool samples, demonstrate an increase in Firmicutes and decrease in Bacteroides. Animal studies of epilepsy suggest that the widely popular and effective ketogenic diet may be effective at reducing seizures by altering the gut microbiota.

In a prospective clinical study, 45 adult participants with drug-resistant epilepsy were provided with a daily probiotic mixture, in addition to their regular medications, for four months (Gomez-Eguilaz et al 2018). The probiotic mixture contained *Streptococcus thermophilus, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subs *bulgaricus, Bifidobacterium breve, B. longus* y *and B. infantis* y CD2. The results demonstrate significant improvement in quality of life as measured by the questionnaire of quality of life in epilepsy and reduction in seizure frequency. Nearly 30% of the participants reported a greater than 50% reduction in seizure frequency.

From a different perspective, another prospective study evaluated the effects of an antibiotic on drug-resistant epilepsy. Ciprofloxacin, a broad-spectrum quinolone, was administered to 23 adult participants for the duration of five days and participants were followed up for a total of 12 weeks to examine the impact. There was significant reduction in seizure frequency ($p<0.001$) that was observed at the end of the first week and was maintained for the remainder of the study. Additionally, there was an increase in the ratio of beneficial Bacteroidetes to Firmicutes (Cheraghmakani et al 2021).

Melatonin

Melatonin is well known for its benefits in the treatment of insomnia. Seizures and insomnia can often coexist and have a bidirectional relationship. Poor sleep quality or lack of sleep may precipitate increased seizure frequency the next day, and seizures themselves may interfere with sleep quality. Several small clinical studies examined the effects of melatonin on seizure frequency.

A small randomized double-blind study of 10 pediatric participants with epilepsy demonstrated improved sleep latency with the use of 9mg of sustained release melatonin after four weeks compared to placebo. There was no measurable improvement or worsening of seizures during this time, demonstrating safety at a relatively higher dose (Jain et al 2015). Another small study of six pediatric participants with neurological deficit disorders in addition to epilepsy demonstrated a positive impact on seizures when melatonin was provided as an adjunct therapy. All six participants had been consistently taking their respective AEDs and were provided with 3mg of melatonin thirty minutes before sleep for three months. Five out of six parents reported reduction in seizures, particularly during the night, as well as general improvement in

communication and daily behaviours (Peled et al 2001). Lastly, a study of 10 pediatric participants with severe epileptic disorder reported better seizure control after one month of nightly supplementation with 3mg of melatonin (Uberos et al 2011).

Melatonin is considered to be a potent antioxidant. Studies on the consequences of epilepsy report higher oxidative stress in unmanaged cases and raise the possibility that epilepsy may be caused or aggravated by increased production of reactive oxygen species (Aguiar et al 2012). A small double-blind study of melatonin in pediatric patients with epilepsy receiving melatonin demonstrated that antioxidant enzymes such as glutathione peroxidase and glutathione reductase are less active in these patients and that melatonin (6-9mg/d) is able to increase their activity (Gupta et al 2004).

Omega-3 Fatty Acids

Adult participants with refractory epilepsy (n=50) were randomized into placebo and omega-3 intervention groups for 16 weeks (Omrani et al 2019). This was a triple-blind study, which included blinding of the patient, neurologist (assessor), and statisticians. The omega-3 capsules were composed of 120mg of DHA and 180mg of EPA and were given twice per day for a total daily dose of 240mg of DHA and 360mg of EPA. The study demonstrated statistically significant improvement in seizure severity (assessed via EEG) ($p=0.034$), reduction in seizure frequency ($p=0.014$), reduction in seizure duration ($p=0.009$) and reduction in TNF-*alpha* and IL-6 inflammatory markers.

Earlier clinical trials show mixed results with a variety of doses, ranging from 112mg of DHA and 171mg of EPA to 5g of combined EPA with DHA (Schlanger et al 2002, Yuen et al 2005), in terms of seizure frequency. There seems to be consistency with respect to impact on inflammatory cytokines and most studies demonstrate seizure reduction. There are several mechanisms of action that are proposed in relation to epilepsy. These include protection of the GABA inhibitory interneurons, stimulation of antioxidant enzymes such as super oxide dismutase and glutathione peroxidase, as well as reduced inflammation.

Vitamin E

A recent clinical trial on vitamin E demonstrates significant improvement in epilepsy management. The double-blind placebo-controlled trial provided 65 adult participants with epilepsy with 400IU of vitamin E per day as *alpha*-tocopherol alone for six months in addition to their AEDs. The intervention resulted in statistically significant reduction in seizure frequency ($p<0.001$) as well as better functioning of the antioxidant enzymes (Mehvari et al 2016). The improvement in seizures may have been due to the improved antioxidant capacity, or due to vitamin E's ability to promote reduction of excitotoxicity, or its anti-inflammatory effects.

Vitamin D

Deficiency of vitamin D has been observed in a variety of neurological, mood, autoimmune, and many other conditions. Not surprisingly it has also been observed in patients with epilepsy (Teagarden et al 2014). However, when it comes to examining the therapeutic effect of

supplementation, the results are mixed. A pilot study (Hollo et al 2012) demonstrates a 40% reduction in mean seizure production after 90 days of supplementation with vitamin D. Participants (n=13) with epilepsy were first assessed for their vitamin D status. Those who had sufficient stores were given a daily maintenance dose of 2,000-2,600IU for the duration of the study. Those with vitamin D levels of <30ng/mL were first given a single oral dose of 40,000-200,000IU of vitamin D and then continued with the daily maintenance dose. Twelve of the thirteen participants were found to be deficient, and six participants were still deficient at the end of the 90-day study, though their levels did improve (Hollo et al 2012).

N-Acetylcysteine (NAC)

The use of NAC in neurology is gaining popularity with a systematic review in 2015 reporting favorable evidence for consideration of the use of NAC in disorders such as Alzheimer's, bipolar disorder, neuropathies, autism, and many others (Deepmala et al 2015). While the theory behind NAC's applicability may be positive, there is a lack of clinical trials on this subject in terms of its use for epilepsy. The closest clinical evidence that is available comes from a case report of four siblings with progressive myoclonus epilepsy. The siblings received a combination of antioxidant vitamins and mineral for six months with mild improvement in their symptoms. After the addition of 4-6g of NAC, there was a large decline in seizures which was maintained for the 30 months of continued supplementation (Hurd et al 1996).

Coenzyme Q10

Continuing on the topic of antioxidants, coenzyme Q10 (CoQ10) is also considered an important antioxidant and may be deficient in patients with epilepsy. An observation study examined the serum levels of CoQ10 in 39 participants with epilepsy and compared these to levels from 35 healthy participants. They found that not only were the levels of CoQ10 significantly lower in participants with epilepsy ($p<0.001$), but they were also correlated with seizure severity and frequency (Simani et al 2020). However, it is unclear whether this is a contributing cause of epilepsy or a consequence. Are the seizures more likely to occur because there is a lack of antioxidant protection and oxidative stress has a direct means of stimulating seizures, or has the body become deficient in antioxidants as a consequence of experiencing frequent seizures which themselves act to produce reactive oxygen species and cause oxidative stress?

Unfortunately, there are no clinical trials that exclusively examine the effect of CoQ10 on seizures. The closest clinical study looked at a combination of vitamins along with CoQ10 on the seizure frequency of adult participants with intractable focal epilepsy (n=30) while taking regular AEDs. This open label study provided participants with a cocktail of 100mg of vitamin B6, 5mg of vitamin B9, 1000IU of vitamin D, 400IU of vitamin E, and 100mg of CoQ10 for six months. There was a significant decline in seizure frequency compared to baseline ($p<0.045$) with an average decrease of seven seizures per month, as well as 12.5% of the participants reportedly being completely seizure free (Chang 2020).

Conclusion

Several nutrients and herbs have demonstrated significant reduction in seizure frequency when provided in addition to standard antiepileptic drugs. While studies discussed in this review demonstrate the capacity for nutrients and herbs to provide additional benefits to medications, there is a significant need for further clinical trials to examine the maximum potential for these treatments, particularly in patients who are unable to tolerate the antiepileptic drugs. The studies reviewed were fairly small in terms of the number of patients and frequently short in duration. Additionally, the types of medications used and the types of epilepsy were all different in these reports. Further research is crucial as there is an important need for effective management of epilepsy.

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Clinical Evaluation of Green Tea (*Camellia sinensis*) as a Respiratory Anti-Viral

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Abstract

Green tea (*Camellia sinensis*) consumption originated in China and has been consumed for thousands of years due in part to its refreshing and pleasant taste and also to its purported health benefits. Over 200 compounds are synergistically present in green tea leaves including polyphenols, L-theanine, caffeine, tannins, and trace elements. Studies have found that polyphenolic compounds can constitute up to 30% of the total dry mass of green tea leaves. Catechins are the most abundant, potent, and well-studied of the polyphenolic flavonoids in green tea. Recent pandemics including influenza in 2009–2010 and the present severe acute respiratory syndrome coronavirus 2 (COVID-19) have put global pressures on the scientific, public health, and medical communities to research and develop other non-pharmaceutical preventative solutions against these infectious respiratory diseases. The aim of this review is to summarize the current clinical trials utilizing green tea as a respiratory anti-viral and bring recognition to non-pharmaceutical interventions (NPI) which hold the potential to decrease the total number of cases, spread, and severity of respiratory infections.

Introduction

Green tea (*Camellia sinensis*) consumption originated in China and has been consumed for thousands of years due in part to its refreshing and pleasant taste and also to its purported health benefits. The health-promoting actions of green tea are far reaching, including anti-oxidative, anti-tumor, anti-microbial, and anti-viral. Green tea has also been shown to have a beneficial impact on multiple diseases including cardiovascular disease (CVD), type-2 diabetes, obesity, and metabolic syndrome, breast, lung, esophageal, stomach, liver, and prostate cancers, psychiatric disorders, and inflammatory joint conditions (Musial et al 2020, Reygaert 2018).

Green tea has gained popularity in the Western world due to its greater concentration of naturally occurring antioxidants and polyphenols than other forms of tea. The preparation of green tea is unoxidized which preserves the polyphenolic constituents present in the leaves and buds of *Camellia sinensis*. Over 200 compounds are synergistically present in green tea leaves including polyphenols, L-theanine, caffeine, tannins, and trace elements. Studies have found that polyphenolic compounds can constitute up to 30% of the total dry mass of the green tea leaves. Catechins are the most abundant, potent, and well-studied of the polyphenolic flavonoids in green tea (Tallei et al 2021). Within a single cup (120 mL) of brewed green tea is an estimated 150mg of green tea catechins (GTC), of which 10 to 15% are epigallocatechin gallate (EGCG), six to 10% are epigallocatechin (EGC), two to 3% are epicatechin gallate (ECG), and 2% are epicatechin (EC) (Rawangkan et al 2021). GTCs have been shown to possess broad spectrum inhibitory viral action against many viruses such as Epstein-Barr virus (EBV), Human Immunodeficiency virus (HIV), Chikungunya virus (CHIKV), Zika virus (ZIKV), Influenza virus, and more (Xu et al 2017).

Recent pandemics including influenza in 2009–2010 and the present severe acute respiratory syndrome coronavirus 2 (COVID-19) have put global pressures on the scientific, public health, and medical communities to research and develop other non-pharmaceutical preventative solutions against these infectious respiratory diseases. Scientific evidence supports GTCs, particularly EGCG, as being an effective anti-viral agent against influenza and SARS-CoV-2 (Umeda et al 2021). In 1993, Nakayama's research lab, was the first to discuss EGCG's ability to inhibit influenza A (IVA) and B (IVB) as they found that the potent catechin was capable of preventing both IVA and IVB from absorbing onto the cell surface as EGCG agglutinated the viral particles while simultaneously preventing hemagglutination thereby blocking the infectivity of the virus (Xu et al 2017). EGCG also acts by inhibiting influenza viral replication by preventing the activity of viral RNA and modulating cellular oxidation-reduction reactions *in vitro* (Umeda et al 2021). As for SARS-CoV-2, Wang and colleagues (2021) tested EGCG's ability to bind to COVID-19 spike protein along with 10 other plant polyphenols. The molecular docking study found EGCG to have the greatest binding affinity to the SARS-CoV-2 spike protein suggesting that it is superior at inhibiting COVID-19 infection of host cells relative to other polyphenols tested (Wang et al 2021). As green tea's anti-viral action continues to be investigated clinically, it is important to note that even at high concentrations, polyphenols have

been shown to be less toxic than other anti-viral drugs as they do not have cytotoxic effects (Tallei et al 2021).

The purpose of this review is to summarize the current clinical trials utilizing green tea as a respiratory anti-viral and bring recognition to non-pharmaceutical interventions (NPI) which hold the potential to decrease the total number of cases, spread, and severity of respiratory infections.

Human Trials of Anti-Viral Action of Green Tea

The search for studies investigating the respiratory anti-viral action of green tea *in vivo* identified 12 publications of interest summarized in **Table 1**. Of the chosen studies, three are observational trials, two are intervention trials, and the remaining seven are randomized-controlled trials (RCTs). The majority of the 12 studies are focused on influenza with publication dates ranging from 2006-2020. During the past two years however, COVID-19 has taken center stage as the pandemic disrupted human living across the globe, and research has quickly caught up producing three clinical trials on green tea and COVID-19 between 2021 and 2022.

Of the 12 publications, three RCTs (Ide et al 2014, Toyoizumi et al 2013, Yamada et al 2007) and one (Yamada et al 2006) intervention trial assessed the effects of gargling with green tea on incidence of influenza. The four studies all took place in Japan but among different populations including high school students (aged 15–17 years), healthy adults (20–65 years old), and elderly (>65 years old) residents in a nursing home. In all studies, the groups were instructed to gargle three times per day over the course of 60–90 days. In three of the four studies, a tendency towards lower incidence of infection was observed in the catechin gargling group, however it was not statistically significant. Yamada and colleagues (2006) found the incidence of influenza among elderly patients in a nursing home was statistically significantly reduced when gargling with the catechin extract over the 90-day study period. While there are many factors, including the patient's age, exposure, and immune function, that make it challenging to compare the outcomes of the four trials. It should be noted that Yamada and colleagues (2006) used a lower total catechin concentration (200μg/mL) than other groups (400μg/mL Yamada et al 2007 and 560μg/mL in Toyoizumi et al 2013), yet the percentage of EGCG was the highest at 60% compared to 18% used by Toyoizumi et al 2013. Additional clinical trials amongst different populations and using various concentrations of catechins and EGCG are needed to determine the effectiveness of gargling with green tea as a prophylaxis for influenza and other viral respiratory infections.

Three observational trials questioned participants about their green tea consumption in order to extract correlative data linking green tea consumption to change in incidence of infection. Two of the studies were performed by the same research group (Nanri et al 2021 and 2022), however the 2021 trial was a case-control study evaluating the amount of green tea consumed in individuals who were diagnosed with influenza (cases) compared to matched controls. In 2022, Nanri and colleagues switched their focus to the ever-present COVID-19, performing a

serological study and questionnaire in healthcare workers to analyze the impact of drinking green tea on incidence of infection in an at-risk population. The third study, conducted by Park et al 2011 found that schoolchildren who consumed 1–5cups of green tea per day had an inverse risk of influenza infection.

While the majority of the 12 publications presented in **Table 1** focused solely on GTCs or EGCG, a pair of RCTs provided participants with capsules formulated with a combination of catechins and L-theanine for the prevention of influenza and URTI. Both Rowe et al 2007 and Matsumoto et al 2011 found subjects in the intervention group had reductions in the symptom picture and clinical incidence of infection. One other trial (Bettuzzi et al 2021) used capsules as the route of administration, however their formulation only evaluated the effects of catechins. While this was a small intervention trial conducted in participants who were infected with COVID-19, all 10 participants were symptom free and fully recovered within the 15-day treatment window.

Of the remaining two studies in **Table 1**, one RCT conducted by Mahdavi-Roshan et al 2022 compared the effects of brewed green tea with black tea (control) on the psychological symptoms of individuals diagnosed with mild-to-moderate SARS-CoV-2. Interestingly, the subjects consuming the green tea reported reductions in fatigue, depression, and anxiety. Lastly, an intervention trial in healthcare workers randomized subjects into one of three (high catechin, low catechin, and placebo) groups. Participants receiving the high-catechin beverage had a statistically significantly lower incidence of URTI than the placebo group (Furushima et al 2019).

Table 1. Human Intervention Trials and Observational Studies of Green Tea as an Anti-Viral

Reference	Methods	Outcomes
COVID-19		
Bettuzzi et al 2021	Ten adult patients swab-positive and symptomatic (cough and fever greater than 38°C) for SARS-CoV-2 received at-home treatment with two sessions of inhalation and three capsules of ThE (total GTC: 840mg of which 595mg were EGCG) per day for 15 days. A CBC and differential along with markers of inflammation including CRP, ESR, and IL-6 were performed on recruitment day (T0) and following symptom relief (T1) – median of nine days later.	All 10 patients were symptom free and fully recovered within the treatment window, with seven out of 10 participants having a negative-COVID swab on a median of nine days from starting ThE therapy. Of the five high risk patients who were all over 52 years of age, all saw a statistically significant decrease (*t*-test, p-value < 0.03) in IL-6 following ThE treatment. ESR rates in seven of the 10 patients

		were elevated at T0 and had returned to normal by T1.
Mahdavi-Roshan et al 2022	Forty adults, aged 20 and older, presenting with mild-to-moderate symptoms of COVID-19, confirmed by two positive PCR tests performed via nasopharyngeal or oropharyngeal swabs, were randomized to consume either three cups of green (intervention) or black tea (control) per day for four weeks. Patients' fatigue, anxiety, and depression were assessed using the Chadler Fatigue Scale, Beck Depression Inventory-Fast Screen and State-Trait Anxiety Inventory questionnaires both at baseline and after completion of the intervention.	At four weeks, the green tea intervention group showed statistically significant reductions in fatigue, depression, and anxiety associated with mild-to-moderate COVID-19.
Nanri et al 2022	Staff members (N=2640, 767 men and 1873 women; between the ages of 21 and 75 years old) of a referral hospital in Tokyo, Japan, participated in a serological survey and questionnaire. Investigators measured IgG and total antibodies to SARS-CoV-2 on three survey days over the one-month study period. Participants were also questioned about their green tea consumption.	Green tea consumption was not found to have a statistically significant reduction in SARS-CoV-2 infections. Participants who consumed greater than four cups of green tea per day showed a trend towards lower odds of infection, though not statistically significant.
Influenza		
Yamada et al 2006	One hundred twenty-four residents aged 65 and older of a nursing home in Japan participated in a three-month prospective study to evaluate the effects of gargling green tea extract on prevention of influenza infection. Seventy-six residents (24 men and 52 women) were instructed to gargle a tea catechin extract (comprising of 200μg/mL catechins, 60% EGCG)	The tea catechin group had a statistically significant lower incidence of influenza with only one resident (1.3%) infected compared to five of the control residents (10%) during the three-month study period.

	three times per day over a period of three months. Forty-eight age- and sex-matched controls followed the same instructions but received tea without the catechin extract. The primary outcome compared across the two groups was the incidence of influenza.	
Matsumoto et al 2011	Healthcare workers (N=196) of three elderly care facilities in Higashimurayama, Japan, participated in a five-month study investigating the protective effects of green tea for influenza. Ninety-seven participants (21 men and 76 women; median age of 42.1 years) received capsules with GTC (378mg/day) and L-theanine (210mg/day) compared to 99 participants (23 men and 76 women; median age of 43.2 years) in the placebo group. The primary outcome of the study was the clinical incidence of influenza infection. Secondary outcomes gathered included influenza viral antigen measured by immunochromatographic assay and the period of time which the patient received the intervention prior to influenza infection.	The clinical incidence of influenza was statistically significantly lower in the GTC and theanine group (four participants) compared with the placebo group (13 participants) (adjusted OR 0.25, p-value = 0.022). The intervention group also had a lower rate of laboratory-confirmed influenza; however this was not found to be statistically significant (adjusted OR 0.17, p-value = 0.112).
Park et al 2011	Schoolchildren (N=2050) between the ages of six and 13 attending one of nine elementary schools in Kikugawa City, Japan, participated in a questionnaire about their green tea consumption and personal health status including incidence of influenza infection, household exposure, preventative health measures, and influenza vaccination status.	Consumption of one to five cups of green tea on six or more days of the week supported an inverse association with incidence of influenza. Interestingly, the children who consumed greater than five cups of green tea per day saw no protective benefit against influenza infection.

Rowe et al 2007	Healthy adults (N=124, 52 men and 72 women) between 21 and 70 (average age of 29) years of age were randomly assigned to the green tea extract (L-theanine and EGCG) capsule or placebo groups. Participants were told to take two capsules per day (once in the morning with breakfast and once in the evening with dinner) over a 12-week study period. A daily symptom log was used to assess cold and flu symptoms, the number of days participants experienced symptoms, and whether medical treatment was sought out. Blood samples were also taken at baseline (day zero) and at day 21 to assess the effect of the green tea capsules on the proliferation of $\gamma\delta$ T-cells and the downstream production of interferon gamma, an antimicrobial cytokine.	Individuals in the green tea supplement group experienced 32.1% fewer cold and flu symptoms (p-value = 0.035), 22.9% fewer days with illness (p-value = 0.092), and 35.6% fewer symptoms days (p-value < 0.002) compared to participants in the placebo group. Additionally, participants in the supplement group proliferated 28% more $\gamma\delta$ T-cells (p-value = 0.017) and secreted 26% more IFN-γ (p-value = 0.046) in response to $\gamma\delta$ T-cell antigens than those taking the placebo.
Nanri et al 2021	Japanese workers (N=4302) participated in an observational study examining the association of green tea consumption and influenza infection. To determine which subjects would represent the cases, workers were questioned about whether they had been diagnosed with influenza by a doctor between the months of November 2011 and April 2012. One hundred eighty-two subjects responded 'yes', however three were excluded, leaving 179 subjects to represent the influenza cases. For each influenza case, two matched controls (353 participants) were randomly selected for analysis. The 532 total participants were divided into three groups based on their green tea	Consumption of green tea statistically reduced the rate of developing influenza (adjusted OR for the group consuming five or more cups of green tea per week was 0.61 compared to those drinking less than one cup of green tea per week, p-value = 0.028).

	consumption – less than one cup per week, one to four cups per week, and five or more cups per week.	
Ide et al 2014	High school students (N=747) ages 15 to 17 years from six high schools in Schizuoka Prefecture, Japan, were randomized to the green tea or water (control) gargling groups. The green tea group (N=384) was instructed to gargle three times per day over the 90-day intervention while the water gargling group (N=363) followed the same procedure with tap water. The adherence rate was 73.7% (N=283) for the green tea group compared to 67.2% (N=244) in the water gargling group. The primary outcome of the study was laboratory-confirmed influenza determined by immunochromatographic assay for detection of influenza viral antigen.	The incidence of laboratory-confirmed influenza among high school students gargling with green tea (19 students; 4.9%) was not statistically significantly different compared to the water group (25 students; 6.9%) (adjusted OR 0.69, p-value = 0.24).
Yamada et al 2007	Healthy subjects (N=404) aged 20 to 65 years where randomly assigned to either the catechin group – gargling with GTC extract containing 400μg/mL of catechins – or the placebo group. Both groups were instructed to gargle three times per day over the 90-day study period. The participants considered in the study analysis were all vaccinated for influenza and included 195 participants in the catechin group and 200 subjects in the placebo group. The incidence of influenza measured by rapid assay from influena viral antigens served as the primary outcome measured.	The GTC group had half the incidence of influenza (two individuals; 1%) compared to the placebo group (four individuals, 2%), however the difference was not statistically significant.
Furushima et al 2019	Healthcare workers (N=255) participated in an RCT assessing the	The incidence of URTI among healthcare workers in the high-

	efficacy of catechins to prevent acute URTIs. Of the 255 workers, 84 were randomized to the high-catechin group (57mg catechins and 100mg xanthan gum dosed three times per day), 85 in the low-catechin group (57mg catechins and 100mg xanthan gum dosed once per day), and 86 in the placebo group (0mg catechins and 100mg xanthan gum). The study was conducted over 12-weeks and the primary objective measurement was the incidence of URTI.	catechin group (11 incidents) was significantly lower than in the placebo group (23 incidents) (OR 0.46; p-value = 0.04). There was no statistically significant difference in the incidence of URTI in the low-catechin group compared to the placebo.
Toyoizumi et al 2013	Students (N=307, mean age of 15.8 years) attending high school in Kakegawa City, Japan, were asked to gargle three times per day with either green tea (total GTC content was 56mg/dL of which 18% was EGCG) or water. Of the total students who began the study, 225 participants adhered to the study protocol, including 119 students in the green tea group and 106 in the water gargling group. The incidence of infleunza infection served as the primary endpoint.	Comparison of the students adhering to the green tea and water groups, the incidence of influenza infection was lower in the green tea group (six participants) than the water group (10 participants), however the difference was not statistically significant (p-value = 0.31).

Abbreviations

CBC = Complete blood count
CRP = C-reactive protein
CVD = Cardiovascular disease
EGCG = Epigallocatechin gallate
ESR = Erythrocyte sedimentation rate
GTC = Green tea catechin
IFN-γ = Interferon gamma
IL-6 = Interleukin-6
IVA = Influenza A virus
IVB = Influenza B virus
NPI = Non-pharmaceutical intervention
OR = Odds ratio

RCT = Randomized-controlled trial
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2
ThE = Theaphenon E
URTI = Upper respiratory tract infection

Discussion

Preclinical studies of green tea have focused on polyphenols and GTCs as they have been shown to have many health-promoting actions. The objective of this review is to present several clinical studies that have been conducted to evaluate the respiratory anti-viral action of catechins, most notably EGCG, following the ingestion of green tea. As a potential NPI, the route of administration is important to consider for widespread implementation and thus the efficacy of different routes of administration for green tea consumption, i.e., drinking brewed green tea, supplementing with GTC extract, taking green tea capsules, and gargling with green tea were analyzed. None of the reviewed studies reported any safety concerns with the various interventions investigated.

Of the clinical trials reviewed in **Table 1**, some limitations were apparent, i.e., the size of the population, duration of the study, adherence rate and the possibility of bias due to outstanding confounding and unadjusted confounders, i.e., immune function, underlying chronic diseases, vaccination status, previous and recent viral exposure, dietary intake, etc.

Ide et al 2014 further discussed the limitations present in their study, including that the baseline consumption of green tea in both their intervention and control subjects was 70% consuming 1cup (200mL) or more of the tea per day. Expanding on this limitation, the current clinical research evaluating green tea as an anti-viral, documented in **Table 1**, took place in Japan, a country where 53% of adults report consuming green tea on a daily basis (Kim and Kim 2018). With the majority of the Japanese population already consuming green tea, the benefits of the intervention groups may not be as significant as in a population not taking in green tea on a daily basis. Additional large-scale randomized studies repeated in other populations where current green tea consumption is low would be welcomed.

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The Promising Use of Omega-3 Supplementation in Psychiatric Diagnoses

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The Promising Use of Omega-3 Supplementation in Psychiatric Diagnoses

Abstract

It has been evident that the past few years of the COVID-19 pandemic have challenged many people physically, emotionally, and most of all, psychologically; the increase in prevalence of mental health diagnoses and associated symptoms has resulted in an immense need for integrative mental health management tools due to the numerous side effects of conventional medication, suboptimal reduction of symptoms, and the reluctance of parents to give children conventional medication. Omega-3 polyunsaturated fatty acids (PUFAs) have been effective at alleviating symptoms in various neurological, cardiovascular, and endocrine diagnoses, and more due to their anti-inflammatory nature. Omega-3s are an excellent candidate for therapy in psychiatric diagnoses due to their moderate to high efficacy and lower level of side effects. The goal of this article is to comment on the best dosages, durations, and symptom profiles that have resulted in clinical improvement for schizophrenia, major depressive disorder (MDD), bipolar disorder (BD), and attention deficit hyperactivity disorder (ADHD). This article also highlights mechanisms of action that are relevant and that underlie the utilization of omega-3 PUFAs in a clinical setting, either alone or as an adjunct therapy.

Introduction

It has been evident that the past few years of the COVID-19 pandemic have challenged many people physically, emotionally, and most of all, psychologically; hence, the trend of an increase in psychiatric disease has resulted in a greater need for efficacious therapy. Alongside this is the notion that psychiatric diagnoses can be challenging to treat. While antipsychotic and antidepressant medications are aimed at alleviating psychotic and affective symptoms, the effects are often suboptimal, and come with many unwanted side effects. There seems to be a growing need to supplement conventional treatment with naturopathic options in this group of disorders. Some people are also wary of administering medication to their children (i.e. for ADHD). Given these needs and constraints, there has been an increasing interest and recent research on omega-3 supplementation in psychiatric disorders. The objective of this article is to review effects of omega-3 supplementation on schizophrenia, attention deficit hyperactivity disorder (ADHD), bipolar disorder, and depression.

Associated Mechanisms of Action of Omega-3s in Psychiatric Diagnoses

The average human has an Omega-3 Index (O3I) - a major of EPA and DHA in red blood cell membranes - between two and 20%; an optimal level is said to be eight to 11%, whereby a decreased O3I is associated with an increased risk of psychiatric diagnoses (von Schacky 2021). It is thought that increasing this index via omega-3 polyunsaturated fatty acid (N-3 PUFA) supplementation may confer neuroprotective effects. Several studies have shown that an accumulation of N-3 PUFAs in neural cells may have a positive effect on neuronal function, alongside anti-inflammatory and antioxidant activities (Itua and Naderali 2010, Orr et al 2013). Other activities of N-3 PUFAs include increasing membrane fluidity (Meijerink et al 2013), activating peroxisome proliferator activated receptors, and enhancing neurotrophic support (Kou et al 2008). These multi-faceted mechanisms of action lend support for theories of possible neuroprotective and cognitive benefits in psychiatric disorders.

Overall, collective expertise on the subject has concluded that PUFAs and their mediators carry out the following processes in the central nervous system:

(1) the maintenance of cell structure and function of neurons, glial cells, and endothelial cells,

(2) the modulation of neuro-inflammatory processes and associated biomarkers in blood, and

(3) the regulation of neurotransmission (Bazinet and Layé 2014).

These mechanisms give clarity on the underlying mechanisms of why omega-3s have an impact on mood regulation, symptom control, and cognitive function. This further elucidates how N-3 PUFAs may be a novel and efficacious agent for an array of psychiatric disorders such as depression, bipolar disease, ADHD, and schizophrenia.

A. Molecular Findings for Major Depressive Disorder and Bipolar Disorder

It is thought that decreased levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are one of the causes of certain psychiatric disorders. One meta-analysis of 14 case-control studies showed significant reductions in EPA and DHA in plasma and erythrocytes in subjects with major depression (Lin et al 2010). Another set of studies showed that bipolar patients had significant erythrocyte DHA and/or EPA deficits when cross-comparing them to healthy counterparts (Chiu et al 2003, McNamara et al 2015). The protective function of N-3 PUFAs was examined in patients with BD. DHA and EPA caused increased membrane fluidity, as detected by reductions in a membrane integrity marker T2 values, compared to controls in a four-week study (Hirashima et al 2004). Cross-sectional studies have found that children with a very high risk for mood disorders had erythrocyte EPA and DHA deficits compared with healthy individuals (Clayton et al 2008). Plasma EPA and DHA deficits were also confirmed in those with major depression alongside comorbid anxiety disorders (Liu et al 2013).

B. Molecular Findings for Schizophrenia

Parletta and colleagues found that blood levels of EPA and DHA were reduced in those patients with schizophrenia and depression (Parletta et al 2016). One study showed that those who had taken no medication at the onset of psychosis had erythrocyte DHA and arachidonic acid (AA) deficits compared with healthy individuals (Khan et al 2002). An interesting meta-analysis of 18 case-control studies also showed significantly low levels of DHA and AA in schizophrenic individuals (Hoen et al 2013). These studies have suggested that deficits in erythrocyte DHA and AA may predispose patients to, and persist in those diagnosed with, psychosis.

C. Molecular Findings for Attention Deficit Hyperactivity Disorder

This same logic was used in another meta-analysis of nine cross-sectional studies that found lower blood EPA and DHA levels in children with ADHD compared with healthy controls (Hawkey and Nigg 2014). The rationale behind the use of omega-3 supplementation was an intent to reduce symptoms on a clinical level and correct this deficiency on a molecular level.

Support For the Use of Omega-3s in Schizophrenia

A growing body of evidence exists for the use of omega-3s in schizophrenia, mostly as an adjunct therapy but also alone. One recent randomized, double-blind, placebo-controlled trial (RDBPCT) demonstrated excellent therapeutic potential. Fifty schizophrenia inpatients with a score of >4 on the Modified Overt Aggression Scale (MOAS) who took antipsychotics also received omega 3s (540/360mg EPA/DHA) (N=28) or placebo (N=22) for 12 weeks; MOAS scores (i.e. violence) of participants in the fish oil group declined significantly compared to the placebo group ($t=-2.40$, $P<0.05$) (Qiao et al 2018). A short set of studies suggested that when any dose of omega-3 ethyl-EPA (E-EPA or EPA) was compared with placebo, the need for neuroleptic medication seemed to have been decreased for people that took omega-3 (n=30, 1 RCT, RR 0.73 CI 0.54 to 1.00) and mental state likely improved (n=30, 1 RCT, RR not gaining 25% change in PANSS scores 0.54 CI 0.30 to 0.96, NNT3 CI 2-29) (Joy et al 2000).

A Cochrane Review examined the use of omega-3 and evening primrose oil to treat symptoms of schizophrenia. The review found positive findings of EPA versus placebo for scale-derived mental state outcomes; thus, improved symptoms. It should be noted that the data were preliminary and further studies with more power are needed to confirm the effect to a greater degree. A smaller study within this review looked at using EPA as the only treatment for people hospitalised for relapse. The results showed that EPA may have helped 33% of people avoid using antipsychotic medication for 12 weeks (RR 0.6, CI 0.4-0.91) (Joy et al 2000).

One meta-analysis showed that when individuals in the prodromal state of schizophrenia took omega-3, it reduced psychotic symptom severity and lowered conversion rates to first-episode psychosis. Similar findings were echoed with first-episode schizophrenia; omega-3 lowered non-psychotic symptoms, required smaller antipsychotic medication dosages, and heightened early treatment response rates (Chen et al 2015). One RDBPCT provided clinical value by mention of dosage; 2200mg of N-3 PUFAs or placebo was given for 26 weeks, and the study evaluated symptoms via first-episode schizophrenia. The authors concluded that this dosage was effective as an adjunctive therapy as per the following results: improvement of 50% in symptom severity ($p=0.017$), an improvement in depressive symptoms ($p=0.006$), and a higher level of functioning ($p=0.01$) in the N-3 PUFA group (Pawełczyk et al 2016).

Support For the Use of Omega-3 in Bipolar Disorder and Depression

N-3 PUFAs are thought to be involved in the pathophysiology, treatment, and prevention of bipolar disease (BD) (Sublette et al 2011). A small DBPCT examined the effects of EPA treatment in BD patients as associated with increased brain levels of N-acetyl aspartate (NAA), a marker thought to be active in neuronal integrity. Fourteen female BD patients were given 2g of E-EPA or placebo each day for 12 weeks. The results showed a significant rise in NAA levels in the E-EPA group versus placebo ($p=0.027$), thus establishing grounds for a possible neuroprotective role of N-3 PUFAs in BD that can be corroborated with larger studies (Frangou et al 2007). Several meta-analyses, such as this one, confirmed that omega-3 use as an adjunct therapy in BD helped to reduce the depressive, but not manic symptoms, likely signalling that further research may be needed for a broader scope of symptom analysis (Sarris et al 2012).

A recent study by Li et al confirmed that supplementing with omega-3s for 12 weeks increased blood EPA/DHA levels in depressive patients versus placebo (Li et al 2021). Omega-3 PUFAs have also been proposed to have a beneficial effect when used alongside conventional medication in major depressive disorder (MDD). A meta-analysis demonstrated a beneficial effect of omega-3 PUFAs on depressive symptoms in MDD (standardized mean difference = 0.398 (0.114-0.682), $P=0.006$); the statistics showed a positive correlation between increasing the EPA dose and positive effects on MDD symptoms. EPA was also shown to provide better outcomes in patients taking antidepressants than in those who were taking EPA alone (Mocking et al 2016).

Support For the Use of Omega-3 in ADHD

N-3 PUFAs were also proposed to be useful in the treatment of ADHD. A randomized control trial with supplementation of 500mg per day of EPA and 2.7mg per day of DHA reduced inattentiveness but not hyperactivity (Gustafsson et al 2010). Another study showed that in youth, as measured by parent-rated input, there were decreased symptoms of hyperactivity, inattentiveness, and impulsive behaviour in the treatment group (Sinn et al 2008). One meta-analysis showed that in the primary analyses, N-3 PUFAs did not show improvements in emotional lability (EL), oppositional behaviour, conduct problems, or aggression. However, subgroup analyses of higher quality studies and those meeting strict inclusion criteria found a significant reduction in EL and oppositional behaviour with N-3 PUFA supplementation. This could indicate that larger sample sizes may amplify this effect and show value in highlighting the effects of N-3 PUFAs on reducing EL in subsets of children with ADHD (Cooper et al 2016). A randomized controlled trial showed that supplementation with N-3 PUFAs improved the red blood cell fatty acid profile by significantly reducing AA/DHA in the intervention group when compared with controls (P=0.000) in children with ADHD (Wu et al 2015).

Evidence for omega-3 as an adjunct therapy was shown in an interesting study where individuals (N=90) were randomized to omega-3/6, long-acting Methylphenidate (MPH), or both for one year; ADHD symptoms, as shown by the Clinical Global Impressions-Severity (CGI-S) scale decreased in the omega-3/6 group, compared with a rapid decrease and subsequent slight increase in the MPH group. Also notable is that there were fewer adverse events in the omega-3/6 group and MPH + omega-3/6 group compared to the MPH alone group (Barragán et al 2017).

Clinical Application of Omega-3 in Psychiatric Diagnoses

The summary of clinical benefit appears as follows: It seems that efficacious dosage ranges of omega-3s vary in psychiatric disorders, and based on research, appear to be mainly at >2:1 ratios of EPA to DHA; BD and MDD 1-2g/d for a minimum of 12 weeks, ADHD - youth 500-750mg/d for a minimum of 16 weeks. The dosage of omega-3 used in schizophrenia seems to be approximately 2200mg/day for a minimum of 16 weeks.

As a general dosage overview, studies including a meta-analysis suggest that administration of at least 60% EPA, with total EPA dosage 200-2200mg greater than DHA dosage showed beneficial outcomes in depression (Sublette et al 2011). More specific findings, such as a recent study by Guu et al, suggested that MDD benefitted the most therapeutically from an administration of 1-2g of omega-3s as a ratio of >2:1 of EPA/DHA or just EPA alone (Guu et al 2019).

An additional study indicates clinical value in the following doses and durations for youth with ADHD and MDD. For ADHD, EPA and DHA ≥750mg/d, as well as a larger dosage of EPA (1200mg/d) for those with inflammation/allergy for 16 to 24 weeks. For MDD, it was proposed

that 1000-2000mg/d, designed in a 2:1 ratio of EPA:DHA for 12 to 16 weeks, was effective (Chang et al 2020).

A pivotal point worth delving further into is why EPA, more than DHA, was found to exhibit the anti-depressive effects. Kalkman et al (2021) have attempted to uncover the molecular/pharmacological pathways underlying this phenomenon that parallel the clinical effect. EPA is thought to have a greater role due to its use of the CYP monooxygenase pathway for EPA and EPA-derived eicosanoids, alongside the finding of greater affinity of CB2 and EPA/EPA metabolites versus DHA, and lastly, the incorporation of EPA into phosphatidylinositols, while DHA is mainly incorporated into phosphatidyl-ethanolamine/serine/choline (Kalkman et al 2021). These molecular differences could prove monumental for achieving therapeutic optimization and successful clinical outcomes.

Consideration For Therapeutic Optimization and Future Research

There are several concepts worth noting in the assessment of the use of omega-3s in psychiatric disease prior to personalizing and optimizing a treatment regimen, and for use in further research:

A) The baseline levels in individuals should be examined. Sometimes high levels of improvement are shown only in those with lower baseline levels of EPA/DHA to begin with.
B) The ratio of EPA/DHA is not always stated in the articles, which should be noted in the context of the result shift/outcome of success. A 2:1 ratio has been proposed to be more successful in psychiatric diagnoses than other ratios of EPA/DHA.
C) Consider if the patient has any other comorbidities. Is an equally measurable effect seen if omega-3s are used in individuals with heart disease and depression versus those with depression alone.
D) The practicality of clinical doses of omega-3s from the perspective of compliance in adults and children. Some studies have shown high clinical doses in ADHD that are not likely to encourage compliance in children, also the balance of effective dosing with gastrointestinal and skin-related side effects should be considered.
E) McDonnell et al (2019) showcased that the Omega-3 Index can correspond to an improvement in symptoms. At baseline individuals show significant variation in Omega-3 Index. Achieving an increase of Omega-3 Index of ≥8% resulted in improved health outcomes. While the trial focused on heart disease, it seems appropriate to consider a similar relationship and monitoring of the Omega-3 Index as a tool to guide intervention of N-3 PUFAs for management of mental health concerns.
F) Treatment response markers, such as inflammatory profiles and biomarkers, may determine how responsive an individual is to omega-3s and/or other treatments.
G) How the quality of the supplement might affect the molecular optimization and efficacy.

These questions will enable a more accurate application and understanding of omega-3 use in psychoses prior to designing a therapeutic protocol.

Conclusion

Overall, N-3 PUFAs are thought to be involved in the pathophysiology, treatment, and prevention of BD, ADHD, MDD, and schizophrenia. The clinical value from the studies mentioned above occurs at an average daily dose of 200-2200mg for psychiatric disorders for a duration of 12 to 24 weeks, based on the assessments of research in this article. The mechanisms of action involved are thought to include a low cellular/plasma EPA and DHA level, with the aim of supplementation to correct these lower levels. Further research and future directions of study are required to confirm this effect by designing studies with greater statistical power that could include a thorough examination of EPA: DHA ratios specific to each of these disorders. Nonetheless, many studies have already shown successful adjuvant treatment of omega-3s alongside conventional medicines with improvement at the cellular and clinical level. These findings warrant that omega-3s are a valuable and promising therapeutic candidate for psychiatric diagnoses.

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Towards Establishing Standards of Care of Injection Therapies for Pain Management Delivered by Integrative Healthcare Providers

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Conflict of Interest
TB, MJA, and ADD declare a role in assimilation and delivery of a curriculum educating healthcare providers on ultrasound-guided injection for pain management. ADD declares a physician consultancy role with Bioventus Pharmaceuticals and Clarius Mobile. TB declares a physician consultancy role with Clarius Mobile.

Manuscript Contributions by Author
RO contributed the table showcasing jurisdictions across North America allowing NDs to conduct injection therapies for pain management. TB, MJA, RP, and ADD jointly contributed the remainder of the manuscript.

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Naturopathic doctors practicing interventional orthopedics in provinces and states with a broad scope of practice are perfectly positioned to offer high quality interventional pain management care. Current injection training for NDs varies greatly depending on which state or province they are licensed in. NDs in North America primarily use landmark guided injections of orthobiologics (platelet rich plasma (PRP) and stem cells), prolotherapy, neural, and perineural injections. To further advance our profession in this field, a focus on diagnostic accuracy, competent delivery of image-guided procedural-based interventions, and the addition of hyaluronic acid and the judicious use of corticosteroids is warranted.

Over the last 10 years the scope of naturopathic physicians in North America has markedly broadened. This progression in scope has afforded opportunities for naturopathic doctors to practice non-surgical orthopedic interventions using a variety of orthobiologic and pharmaceutical agents. The most recent naturopathic scope expansion happened in the Northwest Territories (NWT), Canada. As of March 1st, 2022, naturopathic physicians in NWT were given full practicing scope and coverage under the Health and Social Services Professions Act allowing the ability to diagnose and treat pathology, prescription authority, and license to perform in-office minor surgery and interventional orthopedic injection procedures. **Table 1** showcases jurisdictions across North America that allow NDs to perform injection therapies for pain management and various considerations specific to each state/province.

Table 1. Jurisdictions Across North America that Allow Injection Therapies for Pain Management by Naturopathic Doctors

STATE/PROVINCE	JOINT INJ ALLOWED?	TRAINING REQ BY BOARD?	TRAINING HRS (IF REQ)	IMAGE GUIDANCE	ORTHOBIOLOGICS ALLOWED	CONTROLLED SUBSTANCE RX	MINOR OFFICE PROCEDURE	NOTES
Alaska, USA	Yes					No		
Alberta, Canada	Yes	Yes	24	No	No	No	No	Prolotherapy only
Arizona, USA	Yes	No		Yes	Yes	Limited	Yes	SCNM, Residencies
BC, Canada	Yes	Yes	24	Yes	Yes	No		WCIT
California, USA	Under Supervision			Under Supervision		Under Supervision	Under Supervision	MD/DO Supervision
Hawaii, USA	Yes				Yes	No		
Idaho, USA	Yes					No		
Montana, USA	Yes				Yes	Limited	Yes	
New Hampshire, USA	Yes					Limited		
North West Territories, Canada	Yes	Yes		Yes		Yes	Yes	
Oregon, USA	Yes	Yes	14 per section	Yes	Yes, with training	Yes	Yes	NOMA, Residencies
Utah, USA	Yes			Yes	Yes	No	Yes	
Vermont, USA	Yes			Yes	Yes	Limited, with endorsement	Yes	
Washington, USA	Yes			Yes	Yes	Yes	Yes	

Abbreviations

Joint Inj Allowed?: Are joint injections allowed in this state or province by NDs?
Training Req By Board?: If joint injections are allowed, does the governing board require training before the ND performs joint injections?
Training Hrs (If Req): If training is required, how many hours?
Image Guidance: Are NDs allowed to use ultrasound or fluoroscopy to guide the needle when they do joint injections?
Orthobiologics Allowed: Are NDs allowed to harvest and/or use injectate made from the patient's own blood products, such as platelet-rich plasma, micronized fat, or bone marrow aspirate concentrate? Some jurisdictions may allow one or more of these injectates and may or may not allow the harvesting of such injectate.
Controlled Substance RX: Are NDs allowed to prescribe controlled substances in any capacity? This varies based on state/province.
Minor Office Procedure: Are NDs allowed to perform in-office minor surgical procedures, as outlined by the statutes written by each jurisdiction's board?
Notes: May include information about residencies, advocacy groups, special rules, or anything else.

As the naturopathic scope continues to broaden and the number of professional registrants grows, the need for standardization in diagnostic training, image guidance, and interventional pain protocols would benefit the profession. These standards will help to ensure that naturopathic doctors use evidence-based interventions, maintain public safety, and optimize therapeutic outcomes.

Enhancing the fundamental skill set of professionals requires agreement between all stakeholders, including institutional support from both private and public entities and interprofessional collaboration for the development and delivery of standardized protocols. In the absence of standardized application of current evidence-based protocols, it might be easy for the naturopathic profession to settle into long-held approaches for treating pain that have more to do with tradition and historical lack of pharmaceutical access than delivering comprehensive interventional orthopedic care.

As licensed and regulated healthcare providers, naturopathic doctors are able to communicate a diagnosis to patients using case history, clinical presentations, and use of laboratory and imaging modalities. To ensure therapeutic success, the importance of an accurate diagnosis should be the primacy of all healthcare providers prior to treatment. Providers unsure of their diagnosis should work with the patient to formulate a plan to get to a diagnosis through a diagnostic injection, further exam or imaging, or referral to another provider.

Point-of-care ultrasound (POCUS) can assist with both in-office assessment and procedural intervention. Ultrasound is not a replacement for traditional diagnostic imaging, however, it is useful on superficial tissues such as for subacromial bursa and rotator cuff assessment. Ultrasound is superior for needle guidance yielding improved accuracy, safety, and efficacy (Lee and Griffith 2019, Lin et al 2021, Strakowski and Visco 2019).

The use of image guidance for therapeutic injection began to receive significant research attention approximately a decade ago. The theoretical advantage of image guided injections was obvious, yet concerns were raised that the strategy would be blindly adopted without proper rigor in evaluation of relative efficacy to the standard of care- landmark guided injection (Bloom et al 2012, Rathmell et al 2012, Sage et al 2013). The past decade has witnessed hundreds of human trials comparing safety and efficacy of image guided versus landmark guided injection for pain management. Numerous meta analyses have concluded that image guided therapy is superior to landmark guided (Fang et al 2021, Gutierrez et al 2016, Hoeber et al 2016, Li et al 2014, Rimeika et al 2021, Sakellariou et al 2017, Wang et al 2021, Wu et al 2015, Yang et al 2021).

The American Medical Society for Sports Medicine published a position statement in 2015 addressing ultrasound guided injection therapy for pain management. Ultrasound guided injections were concluded to be more accurate than landmark guided injections (Evidence Rating=A), more efficacious (Evidence Rating=B), and required to perform many new procedures (Evidence Rating=C) (Finnoff et al 2015). The orthopedic use of corticosteroids is underutilized in the naturopathic profession despite there being a large body of evidence for its clinical utility and its ubiquitous use in conventional care (Ayub et al 2021, Chen et al 2019, Jiang et al 2020, Jüni et al 2015, Marsland et al 2014). The judicious use of steroids should play an important role in interventional orthopedic practice, for example, in the case of a person living with chronic pain while waiting for replacement arthroplasty (McMahon et al 2013 Pereira et al 2016). A corticosteroid injection can also be very helpful as a diagnostic injection, reducing

inflammation and pain long enough to help identify the source of pain generation. Further, many patients are not interested in getting numerous injections over multiple treatments of prolotherapy or PRP for reasons of cost and comfort. While corticosteroids certainly come with risks, most notably accelerated tissue degeneration, banishing them from an interventional orthopedic practice translates to helping fewer people.

Hyaluronic acid injections, like corticosteroids, are Health Canada and FDA approved to treat joint pain secondary to osteoarthritis. Hyaluronic acid may reduce inflammation and friction to slow the degeneration of cartilage and bone, making it a prevention-based treatment for those living with osteoarthritic pain (Bannuru et al 2011, He et al 2017). This injectable therapeutic option has demonstrated pain relief in those living with grades 1-3 osteoarthritis in both the hip and knee (McGrath et al 2013). With additional coverage from insurance agencies, this therapeutic can also be a more affordable option than other therapies such as Platelet-Rich Plasma.

In developing this preamble to our joint position statement on injection therapy, we have collaborated with clinicians in the field of interventional orthopedics from a range of disciplines including allopathic medicine, chiropractic medicine, physiotherapy, and naturopathic medicine. It is our hope that all stakeholders in naturopathic medicine will join us in advancing the standardization of both physician skills and injection protocols in the naturopathic profession.

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Advancing Standardization of Ultrasound-Guided Injections in North America

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Conflict of Interest
TM, TB, MJA, FJ, ADD declare a role in assimilation and delivery of a curriculum educating healthcare providers on ultrasound-guided injection for pain management. RM declares a role in delivery of physician ultrasound sonography training. ADD declares a physician consultancy role with Bioventus Pharmaceuticals and Clarius Mobile. TB and GF declare a physician consultancy role with Clarius Mobile.

Advancing Standardization of Ultrasound-Guided Injections in North America

Policy Position Title: Advancing standardization of non-surgical orthopedic interventions in North America.

Position Statement: Healthcare professionals providing in-office interventional pain therapy procedures should be guided by evidence-based practices.

Background: The current landscape in North America estimates 20.4% of Americans experience chronic pain (Dahlhamer et al 2016). With the increasingly aging population and the opioid epidemic claiming the lives of 750,000 people since 1999, healthcare providers must consider alternatives for pain intervention (US Department of Health and Human Services 2010). Office-based landmark-guided corticosteroid injections have been a mainstay in addressing patients' needs for pain relief. While there is a time and place for the use of injectable corticosteroids, there have been many recent advances in the field of interventional orthopedics, including orthobiologic cell therapy and injectable hyaluronic acid. Interventional orthopedics asserts that responsible interventions include an accurate diagnosis and development of a comprehensive, target-specific treatment plan preceding intervention. Further, clinicians should choose the correct therapeutic agent for the patient and condition being treated and use ultrasound and/or fluoroscopy image guidance to ensure patient safety and efficacy of the injection. The cost of point-of-care ultrasound has decreased dramatically making it affordable for clinicians in private practice. There is overwhelming evidence that image-guided injections are more safe, accurate, and effective than landmark-based injections. The evidence clearly suggests that office-based injections therapies should be image guided and the interventionist should be properly trained using image guidance (Chen et al 2006, Cunnington et al 2010, Daniels et al 2018, Evers et al 2017, Hall and Buchbinder 2004, Koutsianas et al 2016, Naredo et al 2004, Rutten et al 2007, Sibbitt et al 2009, Zingas et al 1998).

Policy Position:

Ultrasound or fluoroscopic guidance should be the foundation for practicing competent interventional orthopedics in the evidence-based, case-appropriate delivery of corticosteroids, orthobiologic cell therapy, hyaluronic acid, and prolotherapy.

Recommendations:

1. Interventional orthopedic training should be founded in evidence-based established procedures. Each intervention has specific clinical utility and clinicians should be trained in what to use, when, and where, for best outcomes.

2. Ultrasound-guided injections are more accurate, safe, and effective than landmark-guided injections (Korbe et al 2015, Li et al 2019). Diagnostic ultrasound is an invaluable tool to be used with physical exam, special testing, imaging, and thorough patient history (Wang et al 2021). Hence, clinicians performing orthopedic injection therapies should be trained in the use of diagnostic ultrasound and image-guided ultrasound injections.

3. Educating patients about the scope of treatment options, including cost, and providing realistic expectations about treatment outcomes is paramount to the therapeutic relationship.

4. Adjunctive therapies including topical pharmaceuticals (Huang et al 2015), physiotherapy, bracing (Blankstein 2011), and other manual therapies (McLenon and Rogers 2019) should be considered once an accurate diagnosis has been obtained. Adjunctive therapies then can be deployed appropriately. Injection therapy may be the most efficacious advent to treatment based on diagnosis.

5. Clinicians should be trained and equipped to effectively manage sterile/clean procedure protocols and post-procedure care and adverse reactions. Best practices for healthcare providers involve pre-treatment discovery of possible contraindications, full disclosure to patients of risks, benefits, and advantages of proposed treatment, post-procedure follow up visits, and maintaining communication.

6. It is essential that those doing injection therapies have the judgment to know when to refer to a qualified and trained interventional radiologist skilled in musculoskeletal anatomy and pathology or surgeon when indicated.

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